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Radiation-Induced Skin Carcinomas of the Head and Neck

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Radiation exposures to the scalp during childhood for tinea capitis were associated with a fourfold increase in skin cancer, primarily basal cell carcinomas, and a threefold increase in benign skin tumors. Malignant melanoma, however, was not significantly elevated. Overall, 80 neoplasms were identified from an extensive search of the pathology logs of all major hospitals in Israel and computer linkage with the national cancer registry. Radiation dose to the scalp was computed for over 10,000 persons irradiated for ringworm (mean 7 Gy), and incidence rates were contrasted with those observed in 16,000 matched comparison subjects. The relative risk of radiogenic skin cancer did not differ significantly between men or women or by time since exposure; however, risk was greatest following exposures in early childhood. After adjusting for sex, ethnic origin, and attained age, the estimated excess relative risk was 0.7 per Gy and the average excess risk over the current follow-up was $0.31/10^4$ PY-Gy. The risk per Gy of radiation-induced skin cancer was intermediate between the high risk found among whites and no risk found among blacks in a similar study conducted in New York City (Shore *et al., Radiat. Res.* 100, 192–204, 1984). This finding suggests the role that subsequent exposure to uv radiation likely plays in the expression of a potential radiation-induced skin malignancy.

INTRODUCTION

From as early as 1902 *(1),* there have been case reports and hospital series of radiation-induced skin cancer *(2–9).* While very high doses have been linked conclusively to skin cancer, few investigations have been able to quantify this risk in terms of absorbed dose to skin, and it is not clear whether low or moderate exposures are carcinogenic. Shore and colleagues *(10, 11)* have studied radiation-associated skin malignancies in 2200 children irradiated for ringworm of the scalp compared to 1400 children treated with other modalities. They have reported a relative risk of 3.8 and an absolute risk of $2.3/10^4$ persons per year per Gy at an average skin dose of 4.5 Gy *(10).* The association between radiation and skin cancer was seen only among whites, suggesting that an interaction with ultraviolet radiation might be important. An increase in skin cancer, mostly basal cell carcinoma, has also been found among children irradiated for an enlarged thymus gland *(12),* radiologists *(13, 14),* and uranium workers *(15),* but not among patients irradiated for ankylosing spondylitis *(16),* tuberculosis *(17),* or postpartum mastitis *(17).* Initial reports from the studies of the A-bomb survivors showed no increased risk of skin cancer *(18).* However, a recent report by Sadamori *et al. (19)* suggested a relationship between skin cancer incidence and distance from the hypocenter in Nagasaki, although not for those closest to the detonation.

The Israel tinea capitis study offered the chance to evaluate skin cancer incidence in relation to radiation dose to the scalp, temporal patterns over approximately 25 years of follow-up, and possible effect modifiers. In addition, this study provided the opportunity to study radiation effects in a population of medium skin color that had extensive exposure to uv radiation.

MATERIALS AND METHODS

Study population. The study population consists of 10,834 persons who received X-ray therapy for tinea capitis between 1948 and 1960; 10,834 nonirradiated population subjects; and 5392 nonirradiated siblings (Table I). All of the irradiated subjects were less than 16 years old at treatment. Study subjects either immigrated to Israel from Africa or Asia (mostly the Middle East) or were born in Israel to a father who had emigrated from Africa or Asia. For each irradiated subject, a nonirradiated, tinea-free subject matched on sex, age (±2 years), country of birth, and year of immigration to Israel (±1 year) was chosen from the general population using the Central Population Registry. For 50% of the irradiated subjects, a nonirradiated, tinea-free sibling matched on age (±5 years), country of origin, arid year of immigration (±1 year), with preference given to siblings of the same sex, was also selected. An evaluation of passport control and Population Registry data in 1982 suggests that about 5% of the study population has emigrated from Israel. The percentage of persons emigrating did not differ significantly among the three study groups.

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TABLE I
Study Population and Follow-up Characteristics

Number of subjects	
Irradiated	10,834
Population comparisons	10,834
Sibling comparisons	5,392
Total	27,060
Mean age at irradiation	7.1 years
Range	<1–15 years
Follow-up period	1950–1980
Mean follow-up	24.5 years
Mean dose to scalp	
Single treatment	6.1 Gy
All treatments	6.8 Gy
Method of tumor ascertainment	Nationwide pathology record search and computer linkage with national cancer registry

Tumor ascertainment. Hospital pathology records were searched to identify nonmelanoma skin cancer and benign skin neoplasms of the head and neck area diagnosed between 1950 and 1980. Specially trained abstractors searched the pathology logs of each of the 22 hospitals with pathology departments in Israel. Names and identifying data for every patient with a biopsy indicating a malignant or benign neoplasm of the head and neck area diagnosed between 1950 and 1980 were recorded. Over two million pathology reports were reviewed, of which 59,000 either met the age and ethnic origin criteria of the study or had insufficient demographic or clinical data for the determination of eligibility. These records were abstracted, computerized, and linked to the study cohort. Finally, the entire roster of study subjects was linked to the Central Population Registry which records the vital status of each Israeli citizen and permanent resident. All but one subject were successfully matched and date of death was abstracted for deceased study subjects. Cause of death was obtained from the Registry files. Three melanoma patients were identified through death certificates as well as through the Cancer Registry or hospital search.

Tumors were classified according to the oncology guidelines of the International Classification of Diseases for Oncology *(20)* and included topography code 173 and behavior codes 0–3. The nonmelanoma skin cancer category included basal cell carcinoma (morphology codes 8090/1,3–8095/3), squamous cell carcinoma (8070/3–8081/2), and epithelial cell cancer (8010/3). The benign skin category included benign sweat gland adenomas (8400/0), basal cell benign tumors (8096/0–8110/0), dermatofibromas (8832/0), benign nevi (8720/0–8790/0), and skin cylindromas (8200/0).

Dosimetry. Patients received radiotherapy according to the Adamson-Kienbock technique, a five-field treatment of the scalp, with lead shielding on the face and neck. Patients were treated at four centers, using X-ray machines with beams of 70–100 kVp, 0.5 mm Al filter, and 1.0 mm Al half-value layer used for irradiation of superficial tissues. One course of therapy typically involved 375 roentgens in air to each field, delivered on 5 consecutive days. The prescribed exposure ranged from 350 to 400 roentgens, depending upon the treatment center. About 9% of the patients received two or more treatments. Detailed reports of the Israeli treatment techniques and dosimetry have been published *(21, 22).*

Scalp doses were estimated for individual patients, based on data measured by Schulz and Albert *(23).* Their measurements, expressed as exposure in air at the skin surface, were made using an anthropomorphic phantom representative of a 6-year-old child, duplicating treatment conditions. For this study, these measurements were converted to absorbed dose to the skin. Because the absorbed doses varied widely at different scalp locations, the minimum, maximum, and average doses for each patient were calculated, depending upon the number of courses of therapy that the patient received and the prescribed radiation techniques used at the center where treatment occurred. Dose-response analyses were based on each individual's average scalp dose.

For children receiving one course of therapy the average dose to the scalp was 6.1 Gy (range 5.5 to 6.7). The mean of the individual minimum and maximum doses was 4.4 and 7.8 Gy, respectively. Including patients who received more than one course of therapy, the estimated mean average dose was 6.8 Gy (range 5.5 to 24.4 Gy).

Statistical analysis. The analyses focused on basal cell carcinomas (BCC) because the number of non-basal cell carcinomas and benign skin tumors was small. The data for BCC were cross-classified by sex, ethnic origin (Israeli-born, African-born, Asian-born), age at exposure (0–4, 5–9, 10–15 years), time since exposure (0–4, 5–9, ⋯ 30+ years), calendar time (1950–54, 1955–59, ⋯ 1975–80), scalp dose in Gy (0, 5.5, 6.1, 6.7, 11.4–24.4), and number of X-ray treatments (1, 2, 3+). For each stratum person-years, tumor counts, person-year-weighted average values for dose, attained age, age at exposure, and time since exposure were computed. There were 2670 data cells with at least one person at risk.

Person-years of observation were computed from the date of first treatment for tinea capitis, or the equivalent date for the matched comparison subjects, until the date of tumor diagnosis, date of death, or the study end of follow-up date (December 31, 1980), whichever occurred first. Altogether, 662,950 person-years of observation were accrued with a mean follow-up time of 24.5. Because radiation-induced skin neoplasia likely have at least a l0-year latent period *(10, 24),* the first 10 years of follow-up were excluded from the detailed analyses, leaving 393,220 person-years of observation.

Poisson regression methods were used to compute maximum likelihood estimates for both relative and absolute excess risks *(25).* Parameter estimates, likelihood-ratio tests, and likelihood-based confidence intervals *(26)* were computed using AMFIT, a program for the analysis of general rate models with grouped cohort data *(27).*

Various factors which might affect the risk of skin neoplasia were considered in the models used in these analyses. These factors include sex, attained age, age at exposure, time since exposure, ethnic origin, and radiation dose. If we let $\lambda(z,d,\beta)$ represent the risk of skin cancer as a function of various covariates, including time, denoted by z, radiation dose, by d, and parameters to be estimated by β, the additive relative risk model used for most of these analyses can be written as

$$\lambda(z,d,\beta) = \lambda_0(z_0,\beta_0)\,[1 + \delta(d,\beta_d)\,\varepsilon(z_e,\beta_e)],$$

where the functions $\lambda_0(\cdot)$, $\delta(\cdot)$, and $\varepsilon(\cdot)$ describe the background rates, dose-response function, and effect modification, respectively, the covariate vectors z_0 and z_e are not necessarily distinct.

The background rates and effect modification were modeled as log-linear functions, i.e., $\exp(\beta z)$. The dose–response function was modeled as a linear function of dose; however, in testing for an exposure effect, a binary

TABLE II
Risks of Skin Tumors of the Head and Neck among Irradiated and Comparison Subjects

Tumor type	Irradiated subjects	Comparison subjects	Relative risk[a]	Absolute risk[a] (per 10,000 PY)
Melanoma	2	1	3.0 (0.3–33.1)	0.005 (−0.05–0.2)
Nonmelanoma skin cancer	42	15	4.2 (2.3–7.6)	1.2 (0.8–1.7)
Basal cell	41	13		
Squamous cell	0	2		
Epithelial cell	1	0		
Benign skin	14	6	3.5 (1.4–9.1)	0.4 (0.1–0.6)
Sweat gland	5	3		
Basal cell	4	1		
Dermafibroma	2	2		
Nevi	2	0		
Cylindroma	1	0		
Number of subjects	10,834	16,226		
Person-years (PY)	265,070	397,880		

[a] 95% confidence interval in parentheses.

and neck melanomas were found among the irradiated subjects compared to one among the nonirradiated comparisons (RR = 3.0; 95% CI = 0.3–33.1; absolute risk = 0.005 per 10,000 person-years; 95% CI = –0.05–0.2). Forty-two nonmelanoma skin malignancies occurred among the irradiated subjects, compared with 15 among the two comparison groups combined (RR = 4.2; 95% CI = 2.3–7.6; absolute risk = 1.2 per 10,000 person-years; 95% CI = 0.8–1.7). Among the carcinomas in the irradiated subjects, all but one (98%) were of the basal cell type. Among the nonirradiated patients, 13 of the 15 (87%) were basal cell tumors. Benign skin tumors occurred more than three times more often among the exposed subjects than the nonexposed (RR = 3.5; 95% CI = 1.3–9.1). Benign sweat gland tumors occurred most frequently, but the radiogenic risk was higher for benign basal cell tumors.

Other benign tumors of the head and neck included 6 papillomas, 11 hemangiomas, 15 lipomas, 9 fibromas, 2 myomatous neoplasms, and 2 lymphatic vessel tumors among the irradiated subjects, compared with 13 papillomas, 13 hemangiomas, 4 lipomas, 2 fibromas, 1 myomatous neoplasm, and 1 lymphatic vessel tumor among the comparisons. These data suggest that there may be an increased risk of lipomas and fibromas, but not of papillomas or hemangiomas.

Nonmelanoma Skin Cancer

Among the irradiated subjects the incidence of nonmelanoma skin cancer was 1.6 per 10,000 persons per year of follow-up, compared to 0.4 for the comparison subjects. There were no statistically significant differences in incidence rates by sex or ethnic origin among the comparison subjects (Table III). The mean age at diagnosis of nonmelanoma skin cancer was 27.3 years for the exposed group compared to 30.6 for the nonexposed patients. The mean interval between irradiation and diagnosis (or study entry for the comparison subjects) was 21.6 and 22.6 years, respectively. One epithelial cell and one basal cell carcinoma were diagnosed less than 5 years after radiation treatment. Patients developing benign skin tumors appeared to be slightly younger (mean age at diagnosis = 24.5) and therefore also had a shorter interval between treatment and diagnosis.

Among the exposed patients, 53% of the nonmelanoma skin cancers with known location developed on the scalp, the target radiation area, compared to 36% among the comparisons (Table IV). The location of the benign skin tumors was similar: 50 and 33% occurred on the scalp of the irradiated and nonirradiated patients, respectively.

Basal Cell Carcinoma

To further evaluate tumor risk in relation to radiation dose and effect modification, detailed analysis of the basal cell carcinomas was performed using relative and absolute risk models. These regression analyses were restricted to the 40 irradiated and 13 comparison subjects with BCC diagnosed at least 10 years after irradiation or study entry. After adjusting the background rate for sex, ethnic origin, and attained age, the relative risk of BCC for the irradiated subjects, without regard to radiation dose, was 4.9 (95% CI = 2.6–8.9), while the average excess risk over the current

TABLE III
Selected Characteristics of Nonmelanoma Head and Neck Skin Tumors by Tumor Behavior

	Malignant		Benign	
Characteristic	Irradiated	Comparison	Irradiated	Comparison
Sex (number)[a]				
Male	19 (1.46)	8 (0.40)	2 (0.15)	2 (0.10)
Female	23 (1.70)	7 (0.35)	12 (0.89)	4 (0.20)
Ethnic origin (number)[a]				
African-born	17 (1.09)	9 (0.39)	9 (0.58)	0 (0.00)
Asian-born	15 (2.69)	4 (0.46)	3 (0.54)	4 (0.46)
Israeli-born	10 (1.86)	2 (0.25)	2 (0.37)	2 (0.25)
Age at diagnosis (years)				
Mean	27.3	30.6	24.6	24.3
Range	11–38	17–40	11–34	4–39
Interval between radiation and diagnosis (years)				
Mean	21.2	22.6	18.8	17.5
Range	3–29	12–29	8–25	3–28

[a] Rate per 10,000 persons per year of follow-up in parentheses.

TABLE IV
Anatomical Location of Nonmelanoma Head and Neck Skin Tumors

	Irradiated subjects	Population comparisons	Sibling comparisons
Malignant			
Eyelid	1	0	0
Ear	4	0	1
Face	8	4	2
Neck	4	0	0
Scalp	19	4	0
Unknown	6	4	0
Benign			
Eyelid	1	2	0
Ear	1	0	0
Face	3	0	0
Neck	2	0	2
Scalp	7	1	1

follow-up was 2.0 (95% CI = 1.3–2.6) per 10,000 persons per year.

Effect modification was considered separately for relative and absolute risk models. The background was modeled including effects for ethnicity, sex, and attained age. Background rates increased rapidly with attained age (proportional to the sixth or seventh power of age), but there was little evidence of statistically significant variability with sex and ethnic origin. The relative and absolute models fit the data equally well, but the relative risk model required only one effect modifier (age at exposure) to describe the excess risk adequately, whereas in the absolute risk model, age at exposure, ethnic origin, and time since exposure were all important effect modifiers.

Dose response. An evaluation of risk of BCC in relation to scalp dose demonstrated a significant linear dose response ($P < 0.001$). When number of radiation treatments was used as a measure of dose, a dose response was also seen. Tests for nonlinearity in the dose response, for all subjects and among the exposed subjects only, were not significant. However, because the lowest doses received by exposed subjects are in excess of 5 Gy, these results should be interpreted cautiously.

Using a linear dose–response model, the fitted relative risk for a person irradiated at age 7 rose from 5.4 at 5.5 Gy to 11.3 at 13.0 Gy (Fig. 1). Looking at the adjusted relative risks, the risk appeared to level off in the highest dose group (mean 13.0 Gy).

Age at exposure. Age at irradiation ranged from less than 1 year to 15 years, allowing a limited assessment of age-at-exposure effects. The risk per unit dose of radiogenic BCC increased significantly with decreasing age at exposure. As mentioned above, age at exposure was the only significant effect modifier in the final relative risk model. Under this model, a 5-year decrease in the age at exposure leads to an 80% decrease in the relative risk. Based upon the expected numbers of cancers computed using this model, the fitted relative risks for children irradiated between the ages of 1–4, 5–9, and 10–14 were 19.0, 5.9, and 2.0, respectively (Table V).

Sex and ethnic origin. The relative risk for females was slightly higher than for males; however, the confidence intervals overlapped considerably and the difference in risks was not significant. Although the estimated relative risk for persons born in Israel was substantially higher than for those born in Asia or Africa, this finding was related in large part to the younger age at exposure for the Israeli-born subjects (4.0 for Israeli-born vs 8.0 years for Asian-or African-born) (Table V). When age at exposure was taken into account, place of birth, which is an indicator of ethnic origin, did not appear to be a significant factor in susceptibility to radiation-induced BCC.

Time since exposure. Allowing for a 10-year minimum latent period, there was some evidence of a slight decline over time in the observed adjusted relative risk, however, this trend was not statistically significant ($P = 0.5$) (Table V). In interpreting the results one must bear in mind that in the earlier years of follow-up the risks were very poorly estimated due to the small number of tumors diagnosed, whereas in the 25+ category the estimate was unstable due to the large drop in the number of person-years of follow-up. The fitted risks show that risk remained fairly stable throughout the study period.

The observed and fitted absolute excess risks were very similar until the last period of the study. Based on the small number of person-years available after 25 years of follow-up, the observed risk declined slightly; however, tests for departures from the fitted model provided no evidence against a continual increase over the entire study period

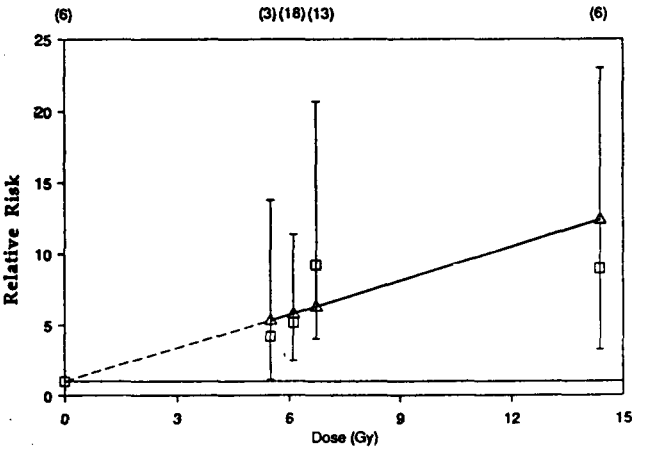

FIG. 1. Observed dose response (□) and confidence bounds (I) for basal cell carcinoma. Point estimates are also presented for the fitted dose response (△). Extrapolation is indicated by the dashed line. Risks are for a person irradiated at age 7. Numbers in parentheses are numbers of exposed cases.

TABLE V
Relative Risk of BCC of the Head and Neck among Irradiated and Comparison Subjects, by Selected Factors[a]

Factor	Irradiated		Comparison		Observed relative risk[b,c]	Fitted relative risk[b,c]
	No. tumor	PYR	No. tumor	PYR		
Age at exposure (years)						
0–4 (Mean = 3.2)	13	43,060	0	75,380	∞ (9.6–∞)	19.0 (14.4–28.4)
5–9 (Mean = 7.3)	24	82,280	9	102,110	3.4 (1.6–7.7)	5.9 (3.3–11.0)
10–15 (Mean = 12.3)	3	31,770	4	58,620	1.4 (0.3–6.2)	2.0 (1.3–4.0)
Sex						
Male	18	77,220	7	118,700	3.7 (1.8–9.6)	5.4 (3.4–9.5)
Female	22	79,890	6	117,410	5.2 (2.3–14.3)	5.8 (3.7–10.1)
Ethnic origin						
African[d]	17	92,200	8	137,010	2.9 (1.3–7.1)	4.8 (3.0–8.7)
Asian[d]	13	34,400	4	53,680	4.8 (1.7–17.0)	4.5 (2.8–8.2)
Israeli[d]	10	30,510	1	45,420	15.2 (3.0–290)	13.7 (10.0–21.0)
Years since exposure						
10–14	3	53,630	0	80,500	∞ (1.5–∞)	4.9 (3.1–8.8)
15–19	6	53,220	1	80,030	9.2 (1.6–170)	5.6 (3.6–8.8)
20–24	25	41,860	8	62,880	4.4 (2.1–10.5)	5.8 (3.7–10.1)
25+	6	8,400	4	12,700	2.3 (0.6–8.9)	5.4 (3.4–9.6)

[a] Excluding the first 10 years of follow-up.
[b] Adjusted for the effects of sex, ethnic origin, and attained age on the background rates.
[c] 95% confidence interval in parentheses.
[d] Mean age at exposure for African, Asian, and Israeli subjects is 7.8, 8.6, and 3.9, respectively. The difference in risk estimates for Israeli- and non-Israeli-born subjects reflects the difference in the mean age at exposure.

(Fig. 2). A time-dependent excess risk model with allowance for dose-effect modification by ethnicity and age at exposure suggests that the excess risks are increasing proportional to time since exposure to the fourth power. For example, at 10 years since exposure the excess risk was estimated to be increasing by about 50% per year, while at 20 years postexposure, the risks were increasing by about 20% each year.

DISCUSSION

Moderate levels of ionizing radiation used to treat tinea capitis in childhood (mean 6.8 Gy) significantly increased the risk of basal cell carcinomas. The relative risk at 1 Gy was estimated as 1.7 and the absolute excess as $0.31/10^4$ PY-Gy. The excess risk of BCC during the period from 10 to 30 years after irradiation in childhood is best described by a linear dose–response model in which the relative risk varies inversely with age at exposure but is constant over time since exposure and does not differ with sex. The best-fitting relative risk model is $RR(d, a) = 1 + 0.28\, d \exp[-0.34(a - 10)]$, where d is dose and a is age at exposure. However, although a dose–response relationship was suggested, it also should be stressed that because no skin doses were below 5 Gy, we cannot address the possibility of a threshold effect for skin cancer based on our results. Although our study provided the opportunity to quantify the risk of BCC according to estimated radiation dose to the scalp, it should be pointed out that tumors also occurred on the face, neck, ear, and eyelid. Unfortunately, the tumor location information was imprecise, and therefore it was not possible to estimate the dose to the tissue in the actual location of the tumor.

Risk appeared to level off in the highest dose group. Although the risk in this group was not significantly different

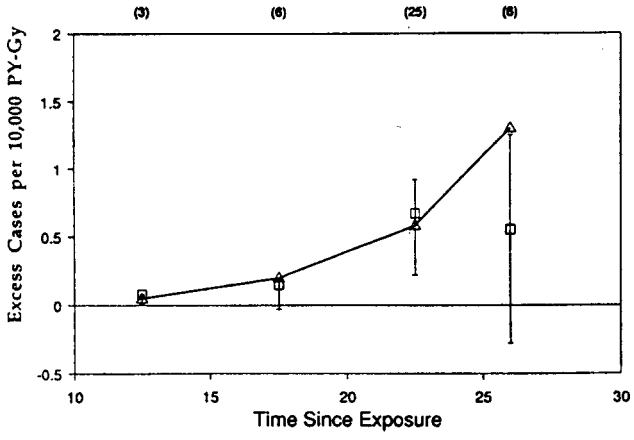

FIG. 2. Observed excess risks (□) and confidence bounds (I) for basal cell carcinoma per 10,000 PY-Gy over time. Observed excess risks are adjusted for ethnicity and age at exposure. Point estimates are also represented for the fitted excess risks (Δ). Numbers in parentheses are numbers of exposed cases.

from those in the lower dose categories, laboratory studies suggest that the addition of uv radiation to ionizing radiation can result in fewer tumors at higher doses *(28).* Burns and Albert *(28)* postulate that in rats very high doses of uv radiation may result in sterilization.

Age at irradiation ranged from less than 1 year to 15 years, allowing a limited assessment of age-at-exposure effects. However, the risk of radiogenic BCC per unit dose increased significantly with decreasing age at exposure. These results, taken in conjunction with findings from anal-

ing skin cancer and hypothesized that uv radiation is an important cofactor for radiogenic skin cancers. Albert and Shore *(17)* suggest that the low sensitivity of darker-skinned people to uv radiation may explain the lack of radiation-induced skin tumors among blacks in the New York tinea study and Japanese A-bomb survivors. Stern *et al. (30)* found that patients who sunburn easily and tan poorly have a higher risk of developing skin cancer after treatment with methoxsalen and long-wave ultraviolet radiation (PUVA) than those with skin types which rarely sunburn and tan well. Burns and Albert *(28)* demonstrated that uv radiation enhanced the induction of skin cancers at relatively low doses of ionizing radiation in experimental settings. Our data also suggest that exposure to sunlight is an important ingredient in the development of radiation-induced BCC at moderate skin doses, since the Israeli population had an intermediate excess risk.

Scotto *et al. (31)* reported that U.S. males are at greater risk of nonmelanoma skin cancer than females. We found a slightly higher cumulative incidence of nonmelanoma skin cancer among the nonexposed male subjects (male to female ratio = 1.1). Although we found no statistically significant effect modification by sex, among exposed subjects the male to female ratio decreased to 0.8.

A major strength of our study is the method of tumor ascertainment. Basal cell carcinomas are difficult to ascertain because they are usually nonfatal and are not reported to tumor registries. Most studies, therefore, rely on self-reporting through questionnaires and can be subject to over- or underreporting biases. The Israeli study obtained information on skin tumor incidence by an intensive search of the pathology records of the 22 general hospitals in Israel. Records of patients fitting the age criteria for the tinea capitis study were abstracted, and this roster of potential study subjects was then linked by computer to the study file, while exposure status was still unknown. This method is advantageous for several reasons: there is complete tumor ascertainment; there is little chance of bias due to overascertainment among the exposed; there is no recall bias as is often associated with questionnaire information; and because all tumors were surgically removed there is confirmation of all diagnoses.

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